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Treatment of Cancers

The present invention relates to the treatment of cancers.

US Patent 5,089,273 relates to compounds identified as ecteinascidins. In particular, it relates to ecteinascidins 729, 743, 759A, 759B and 770. The compounds are disclosed to have antibacterial properties and some are also useful as antitumor agents.

We have now found that ecteinascidin 743 has exceptional activity in the treatment of sarcomas, mesotheliomas and cartilage tumours. A sarcoma is a cancer arising from connective tissue such as muscle or bone. A mesothelioma is a tumour of the mesothelium of the pleura, pericardium or peritoneum.

Thus, the present invention provides a method of treating any mammal, notably a human, affected by a sarcoma, mesothelioma or cartilage tumour which comprises administering to the affected individual a therapeutically effective amount of ecteinascidin 743, or a pharmaceutical composition thereof. Examples of human sarcomas to be treated include osteosarcomas and soft tissue sarcomas, leiomyosarcomas, fibrosarcomas and mesotheliomas.

The present invention also relates to pharmaceutical preparations, which contain as active ingredient ecteinascidin 743, as well as the processes for its preparation.

Examples of pharmaceutical compositions include any solid (tablets, pills, capsules, granules, etc.) or liquid (solutions, suspensions or emulsions) with suitable composition or oral, topical or parenteral administration, and they may contain the pure compound or in combination with any carrier or other pharmacologically active compounds. These compositions may need to be sterile when administered parenterally.

Administration of the composition of the present invention may be by any suitable method, such as intravenous infusion, oral preparations, intraperitoneal and intravenous

administration. Intravenous delivery may be carried out over any suitable time period. We prefer that infusion times of up to 24 hours are used, more preferably 2-12 hours, with 2-6 hours most preferred. Short infusion times which allow treatment to be carried out without an overnight stay in hospital are especially desirable. However, infusion may be 12 to 24 hours or even longer if required. Infusion may be carried out at suitable intervals of say 2 to 4 weeks. An example of a 3 hour infusion treatment is given in the abstract by Twelves et al., at the end of this text.

Pharmaceutical compositions containing ecteinascidin 743 may be delivered by liposome or nanosphere encapsulation, in sustained release formulations or by other standard delivery means.

The correct dosage of ecteinascidin 743 of this invention will vary according to the particular formulation, the mode of application, and the particular *situs*, host and tumour being treated. Other factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

The compositions of this invention may be used with other drugs to provide a combination therapy. The other drugs may form part of the same composition, or be provided as a separate composition for administration at the same time or a different time. The identity of the other drug is not particularly limited, and suitable candidates include:

a) drugs with antimitotic effects, especially those which target cytoskeletal elements, including microtubule modulators such as taxane drugs (such as taxol, paclitaxel, taxotere, docetaxel), podophylotoxins or vinca alkaloids (vincristine, vinblastine);

b) antimetabolite drugs such as 5-fluorouracil, cytarabine, gemcitabine, purine analogues such as pentostatin, methotrexate);

c) alkylating agents such as nitrogen mustards (such as cyclophosphamide or ifosphamide);

d) drugs which target DNA such as the antracycline drugs adriamycin, doxorubicin, pharmorubicin or epirubicin;

e) drugs which target topoisomerases such as etoposide;

f) hormones and hormone agonists or antagonists such as estrogens, antiestrogens (tamoxifen and related compounds) and androgens, flutamide, leuprorelin, goserelin, cyprotrone or octreotide;

g) drugs which target signal transduction in tumour cells including antibody derivatives such as herceptin;

h) alkylating drugs such as platinum drugs (cis-platin, carboplatin, oxaliplatin , paraplatin) or nitrosoureas;

i) drugs potentially affecting metastasis of tumours such as matrix metalloproteinase inhibitors;

j) gene therapy and antisense agents;

k) antibody therapeutics; and

l) other bioactive compounds of marine origin, notably the didemnins such as aplidine.

The present invention also extends to the compounds for use in a method of treatment, and to the use of the compounds in the preparation of a composition for treatment of cancer.

Example

A group of 22 sarcoma patients, including soft tissue sarcomas (fibrosarcomas, leyomiosarcomas, mesotheliomas, etc.) and bone sarcomas (osteosarcomas) have been treated at the maximum tolerated dose (MTD) and recommended dose (RD) during phase 1 trials. Patients' characteristics include 10 men and 12 women, median age 52 (17-68) years, all pre-treated with anthracyclines or alkylators with 1 to 4 previous chemotherapy treatments, median performance status (PS) 1 (0-1) (ECOG), median number of metastatic sites 2 (1 to 7) were treated with ET-743. 11 patients were treated at a dose of 1500 mcg/m2 or over during a 24 hour infusion (9 patients into a clinical trial and 2 patients as compassionate use). One patient was treated at 1500 mcg/m2 in the 3 hour infusion study; 3 patients in the daily times five study (1 hour infusion x 5 days) at doses over 1625 mcg/m2 and 7 patients in the 72 hour continuous infusion at doses over 1050 mcg/m2.

In this group of patients the following responses have been observed: six partial responses (2 osteosarcomas, 2 leiomyosarcomas, 1 fibrosarcoma, 1 mesothelioma) 3 of which lasting over 4 months, one minor response and 4 stabilisations (WHO criteria).

An example of the use of Et-743 against chondrosarcoma cells is given in the accompanying abstract by Hornicek *et al.* Other abstracts relate to a possible mechanism of action of Et-743.